

Purpose

To outline the ethical aspects considered by Bellberry HRECs when reviewing extension study applications.

Definition

Extension studies are studies that allow for patients participating in a parent clinical trial to 'roll-over' into a subsequent related study to continue to observe and measure long-term safety, tolerability, and/or effectiveness. The terms extension study and roll-over study are used interchangeably. The names imply an extension of study drug treatment and for the purposes of this discussion, they are studies that follow-on from double-blind randomised controlled drug trials (RCT). The most common design is the **Open-label extension (OLE)** where all participants, regardless of group allocation in the RCT, receive open label study drug.

Guidance

Issues with Open-Label Extension (OLE) Studies

Firstly, there is a concern that a non-responder to the study drug in the double-blind phase would continue on test agent in the OLE. This can occur because the RCT usually is not unblinded before participants enter the OLE. In this case the participant is continuing with the risk of the experimental drug for no possible benefit. It has been argued that a participant cannot give genuine 'informed' consent without knowing their group allocation in the RCT.¹

Secondly, those who received placebo or another comparator in the double-blind phase would be receiving the test agent for the first time in the extension phase. Data on efficacy usually is not available at the time of rollover. Therefore, justification is needed for commencing the test agent and continuing its use often for a lengthy period with little or no evidence of efficacy. Also, it is common that the monitoring frequency at the start of the OLE is less than that at the start of the RCT. Less frequent monitoring for these study drug naïve participants at the commencement of the extension phase is not acceptable.

Thirdly, the Participant Information Sheet for the RCT must be careful to manage expectations that all participants will receive the test agent regardless of their experience in the RCT. This could be seen as an incentive to enter the RCT.

Finally, these issues need to be viewed in the context that *the information from the OLE is not needed for the primary or secondary efficacy outcomes of the RCT.*

It should be noted; an extension study will not be approved until the main study is approved.

Reasons for Open-Label Extension (OLE) Studies

1. To gather further safety data:

It has been presented that pharmacologically expected (on-target) adverse events have most likely been identified in pre-clinical and clinical studies with control groups and that OLEs provide at best a refinement of these data. It was argued further that OLEs are unlikely to provide useful information on rare on-target events or both common and rare off-target / unexpected events. The sample size of an OLE is unlikely to be large enough to detect rare expected or unexpected events. These will emerge post-marketing. Also, it is unlikely that common unexpected events will be quantifiable if they are relatively common in the study population in any case. Myocardial infarction, for example, might be relatively common in the study population and without a control group in the extension study, an increased frequency would go undetected unless the increase was

very large.² Another important point is that the study group is unlikely to represent the clinic patients who will receive the drug post-marketing. Trial participants are usually healthier with fewer co-morbidities and fewer concomitant medications compared with 'real-life' patients. If the submission wishes to argue that the reason for the OLE is to gather data on safety and tolerability, these issues above should be addressed.

2. To provide continued drug access:

At the commencement of an OLE, it is unlikely that the test drug will have been shown to be efficacious. Therefore, the notion that continued drug access will be beneficial for individuals is not always evident. Certainly, there are instances where continued drug access following a randomised controlled trial is acceptable and even desirable. For example, one would not want study drug ceased at the end of a controlled trial period for a cancer study participant whose disease is controlled or a renal transplant patient who has no rejection signs. However, arguing that continued use of a drug when its efficacy is unknown is in the best interests of a participant when there are marketed alternatives, is problematic.

Conclusions

Submission of open label extension studies require justification clearly addressing the points raised above.

References

¹ Taylor GJ, Wainwright P. Open label extension studies: research or marketing? BMJ 2005; 331: 572-4

² Day RO, Williams KM. Open label extension studies: Do they provide meaningful information on the safety of new drugs. Drug Safety 2001; 30:93-105.